



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 21 2002

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Linda Ballai Fischer --
Director, Regulatory Affairs
Elan Pharmaceuticals
45 Horse Hill Road
Cedar Knolls, NJ 07927-2003

Re: Docket No. 01P-0481/CP1

Dear Ms. Fischer:

This letter responds to your petition dated October 16, 2001, asking the Food and Drug Administration (FDA) to require an acceptable in vivo bioequivalence study conducted under fasting and fed conditions as a condition of approval of an abbreviated new drug application (ANDA) for a generic version of Skelaxin (metaxalone) tablets. For the reasons described below, your petition is granted.

On January 30, 2002, FDA granted a citizen petition from Mutual Pharmaceutical Company asking the agency to reclassify metaxalone tablets as a drug product with potential or actual bioequivalence problems (a bioproblem drug), to announce the reclassification in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), and to require an acceptable in vivo fasting bioequivalence study as a condition of ANDA approval. The Agency published a notice in the November 2001 cumulative supplement to the Orange Book stating its conclusion that metaxalone tablets is a bioproblem drug. Therefore, as you request in your petition, the Agency considers the part of your petition requesting that an in vivo fasting bioequivalence study be made a condition of ANDA approval to be withdrawn.

Your request that a fed study be made a condition of approval of an ANDA for metaxalone tablets is based on the results of a study you conducted to learn if food has an effect on the absorption of Skelaxin. The study was a two-treatment, randomized, crossover study in which 42 healthy volunteers were given a single 400-milligram dose of Skelaxin under fasting (10-hour overnight fast) and fed (standard high-fat breakfast) conditions. You state that the study showed that Skelaxin was significantly more bioavailable when administered with food in that the rate (C_{max}) and extent of absorption ($AUC_{(0-t)}$) were increased. You have submitted a supplement to your new drug application for Skelaxin to revise the labeling to reflect the results of the study.

FDA's review of your study showed that the mean $AUC_{(0-t)}$, AUC_{inf} , and C_{max} values were 17.5 percent, 14.2 percent, and 80.4 percent higher, respectively, under fed conditions compared with fasting conditions. An analysis of variance showed a

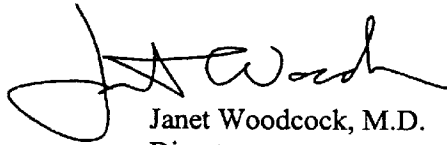
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statistically significant food effect for all three of these pharmacokinetic parameters. Your study also showed that the 90 percent confidence intervals for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, were not within the equivalence limits of 80 to 125 percent for either $AUC_{(0-t)}$ or for C_{max} .

FDA has concluded that because food has a significant effect on the bioavailability of Skelaxin, an ANDA for a generic version of Skelaxin must include an acceptable fed bioequivalence study comparing the generic product with Skelaxin. Therefore, your petition is granted.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'J Woodcock', with a large, stylized initial 'J'.

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research